

# FOREWORD

*by Rudolph E. Tanzi, PhD*

It haunts us with every name we forget: the fear that Alzheimer's is in our future.

For many of us, those lapses will be nothing more than the natural aging process. But for an estimated 5.2 million Americans, Alzheimer's has taken hold—and to most of us in the field, that number is way too low. Millions more die of Alzheimer's-provoked causes, from organ failure to pneumonia. Alzheimer's is a thief that robs you of your memories, your personality, ultimately of your self. It pulls apart the tapestry of who you are thread by thread, until the tapestry just disappears. Cancer is the Big C, but many now overcome it. With the Big A, to date, not one person has survived.

In one sense, we have modern medicine to blame. At the dawn of the twentieth century, our lifespan was forty-nine years. Most of our forebears who carried Alzheimer's-linked genes didn't live long enough to develop the disease. Now many of us live into our eighties: by eighty-five, a third will have Alzheimer's and half will be in the earliest stages of the disease. Nearly 75 million baby boomers are heading that way. Already, Medicare and Medicaid are staggering under the costs. I calcu-

late that by 2020, if the federal government fails to take drastic measures, they may reach a tipping point and start to collapse.

Each year, the federal government spends \$6–12 billion on each of the usual suspects: cancer, heart disease, and AIDS. It spends less than \$500 million on Alzheimer's. Of that, perhaps only \$250 million goes to basic research; much of the rest goes to carrying out large-scale clinical trials for drugs that have, so far, without exception, failed. In his 2015 State of the Union speech, President Obama pledged another \$50 million for Alzheimer's. Unfortunately, it's a Band-Aid on a gaping wound.

Why the shocking lack of funding? One reason is that the young tend to protest more loudly and actively than their parents and grandparents. And of those who have Alzheimer's, how many are likely to be lobbying in Washington about the loss of their minds? But as I warned last year's graduating class at the University of Rhode Island, the young may want to reconsider their lack of interest in Alzheimer's—for almost entirely selfish reasons.

Those graduates will likely live to be eighty-five or ninety years old, if not one hundred. That means more of them—far more—will get Alzheimer's than cancer or heart disease. They may see it as their aging grandparents' problem. In the long run, it's *theirs*. Not only that: they have parents. By their fifties, many of those graduates will hope to have put their own children through college and be spending those later decades traveling the world. No way: not with parents succumbing to Alzheimer's. Through gritted teeth, those graduates will be spending their savings on assisted care and nursing homes and hospice care. Even now, Alzheimer's is not just a disease of the old. It affects us all, and will do so more deeply within the next decade.

Here's the good news. Alzheimer's is probably the most striking example we have among major diseases of a budget-constrained problem. As opposed, that is, to a knowledge-constrained one. We know what we need to do. We have dozens of gene candidates to work on, each one of which can present a new opportunity for drug development. We just lack the money to do that work.

The bad news is that Alzheimer's isn't merely under-represented in funding compared with those other diseases. Those genes we need to look at? Together, we in the field have less than 5 percent of the funding we need to pursue their potential. I'm more fortunate than most; I've published nearly five hundred research papers, and my lab gets serious attention from the National Institutes of Health. Younger scientists in less well-known labs struggle for even the most essential funds to continue. There's so little money in science and research in the United States that more and more students choose not to enter the field. The result: our country faces losing a generation or two of scientists, and all the work they would do. If America does not step up and start funding medical research more seriously, we will rapidly lose our place as a world leader in biomedical discovery. While pharmaceutical companies are needed to bring drugs to the market, the seeds of discovery begin in academic institutions, which depend on federal funding to survive. I am also lucky to be funded by the Cure Alzheimer's Fund (<http://curealz.org>), the most forward-thinking and -looking Alzheimer's research foundation in the world, in my opinion.

Yes, we do at last know which way to proceed. After decades of debate about how Alzheimer's forms in the human brain, we know what the pathologies are, and how they progress, along

with the genes that are responsible. Those genes provoke the creation of amyloid plaques. The plaques then cause so-called tau tangles to form in the surrounding brain cells, eventually to kill those cells. Plaques also cause inflammation, which kills more cells, leading to even more inflammation in a vicious cycle. As our “Alzheimer’s-in-a-Dish” studies have shown, the amyloid sets the fire, if you will, and tangles are the fire that spreads throughout the brain; inflammation fans the flames and makes the fire spread that much faster.

Here’s something else we know now: the amyloid plaques start building up in the brain at least fifteen years before the disease manifests itself. So we know we have to detect plaques far sooner. Then we must have therapies ready to slow them down, akin to lowering cholesterol, if it is too high, to prevent heart disease.

Nearly all of us will develop at least a few of those plaques, though not all of us will get Alzheimer’s. Why? More and more, we think inflammation is key. While plaques and tangles may push you up the mountain, it is inflammation that throws you off the cliff. In the process of inflammation, certain immune cells in your brain kill nerve cells in response to the pathology, leading to a massive loss of nerve cells and the neural circuitry needed for learning and memory.

So we have three mantras going forward: early prediction, early detection, and then early prevention. We will use genetics to predict risk, biomarkers and imaging to detect the disease before symptoms, and then steps to prevent the disease from taking root in those with the strongest propensity to develop it.

We need the right drug, but we also need the right patient—not every one may respond equally to one drug or another.

And we need to know how soon to administer that drug when we do get it. In my lab, we're working on two drugs that seem extremely promising in terms of stopping plaque and tangle growth early on. We are also searching for drugs that will stop the inflammation from spreading. We are lucky to be working with exciting new genetic data about inflammation, obtained from the Alzheimer's Genome Project, also supported by the Cure Alzheimer's Fund.

I wish fervently that I could say to B. Smith and her husband, Dan, that these drugs will reach the market soon enough to keep B.'s Alzheimer's from progressing. I can't. The truth is that at this rate, given the funding we have, our plaque/tangle drug will need another decade in development, the inflammation drug a bit longer than that. If we threw billions more at our research efforts, we could cut that time frame by years. But that's not likely to happen.

For those who have Alzheimer's now, there are lifestyle measures that may allay some symptoms of the disease—measures that B. and Dan report on in this helpful and poignant book. There is also so much that family caregivers can learn about how to deal with Alzheimer's: its many emotional challenges, its hardships, and, if one is looking, the state of grace it sometimes brings.

Alzheimer's is a hard, hard diagnosis to cope with, and I have enormous empathy with those who are doing it. Perhaps it will seem of little comfort to them, but the fact is, I have never been more optimistic about the prospect of treating this disease. It will take time—too much time. Heartbreaking time. But we will get there. Of that, I have no doubt.